Aripiprazole Lauroxil (Aristada): Long-Acting Atypical Antipsychotic Injection Approved for the Treatment of Patients with Schizophrenia

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Schizophrenia is a chronic brain disorder that affects approximately 1% of the US adult population.[1] Schizophrenia is characterized by positive, negative, and cognitive symptoms. Positive symptoms include delusions, hallucinations (eg, hearing voices), and paranoia (eg, the belief that others are controlling your thoughts). Negative symptoms include flat affect, depression, difficulty speaking, and a lack of motivation. Cognitive symptoms include problems with attention, memory, and executive functioning.[1]

In light of its pervasive effects on all areas of personal functioning, the World Health Organization considers schizophrenia one of the most disabling and economically catastrophic medical disorders.[2] The mortality rate among patients with schizophrenia is high; suicide, violent deaths, and a wide range of health problems (eg, cigarette smoking, obesity, diabetes) contribute to the increased mortality rate.[3] Based on health insurance claims data in 2002, the cost of schizophrenia in the United States was estimated at a staggering $63 billion; this included $23 billion in direct healthcare costs (eg, medications, hospitalization), $32 billion in indirect costs (eg, unemployment, reduced work productivity), and nearly $8 million in total direct nonhealthcare costs (eg, law enforcement, homeless shelters).[4]

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Because the etiology of schizophrenia is unknown, the goals of treatment are to eliminate disease-related symptoms and to enhance functioning.[1] The cornerstone of current treatment for schizophrenia is antipsychotic medications, which are available in several forms, including a pill, a liquid, a short-acting injection, or a long-acting injection.[1] After patients have found an effective medication, psychosocial treatment focuses on education and coping skills to prevent relapses and hospitalization.[1]

As of September 2015, a total of 5 long-acting injection formulations of second-generation antipsychotic agents were approved in the United States for the treatment of patients with schizophrenia, including risperidone (Risperdal Consta), intramuscular injection every 2 weeks; olanzapine (Zyprexa Relprevv), intramuscular injection every 2 weeks or every 4 weeks; paliperidone (Invega Sustenna), intramuscular injection every 4 weeks; aripiprazole (Abilify Maintena), intramuscular injection every 4 weeks; and paliperidone (Invega Trinza), intramuscular injection every 3 months.[5-9]

Given the challenges with patient adherence to oral regimens and that relapse leads to serious medical and psychosocial consequences, the future of schizophrenia pharmacotherapy is likely to include improved long-term delivery systems, including intranasal formulations, transdermal patches, subcutaneous implants, and pumps.[10]

Aripiprazole Lauroxil Approved for Schizophrenia

On October 6, 2015, the US Food and Drug Administration (FDA) approved aripiprazole lauroxil (Aristada; Alkermes) for the treatment of adults with schizophrenia.[11,12] Aripiprazole lauroxil is not approved for the treatment of patients with dementia-related psychosis.[12] Aripiprazole lauroxil is a long-acting injection that can be administered every 4 weeks or every 6 weeks, depending on the dose and the location of injection.[12] Using proprietary LinkeRx technology, aripiprazole lauroxil offers multiple dosing options in a ready-to-use, prefilled syringe.[13]

The approval of aripiprazole lauroxil was based on the results of an international, placebo-controlled, phase 3 clinical trial, with >600 patients with schizophrenia. This study demonstrated that aripiprazole lauroxil offers superior symptom palliation compared with placebo.[11,12,14]

According to Mitchell Mathis, MD, Director of the FDA's Division of Psychiatry Products, "Long-acting medications to treat schizophrenia can improve the lives of patients. Having a variety of treatment options and dosage forms available for patients with mental illness is important so that a treatment plan can be tailored to meet the patient's needs."[11]

Mechanism of Action

Aripiprazole lauroxil is a prodrug of aripiprazole, with an unknown mechanism of action.[12] Upon administration, aripiprazole lauroxil converts to aripiprazole, which is a commercially available drug.[13] It is hypothesized that aripiprazole's efficacy is mediated through a combination of partial agonist activity at dopamine D_2 and 5-hydroxytryptamine $(5\text{-HT})_{1A}$ receptors and antagonist activity at 5-HT_{2A} receptors. Actions at other receptors may explain some of the adverse reactions associated with aripiprazole lauroxil, including orthostatic hypotension.[12]

Dosing and Administration

Aripiprazole lauroxil is administered by a healthcare professional via an intramuscular injection into the deltoid muscle (441-mg dose only) or the gluteal muscle (441 mg, 662 mg, or 882 mg). Aripiprazole can be administered as (1) 441 mg, 662 mg, or 882 mg given every 4 weeks, or (2) as 882 mg given every 6 weeks.[12]

In aripiprazole-naïve patients, tolerability should be established with oral aripiprazole before starting treatment with aripiprazole lauroxil. Based on the half-life of oral aripiprazole, up to 2 weeks may be required to fully assess the tolerability to aripiprazole.[12]

After the patient is stabilized with oral aripiprazole, a dosing conversation is recommended (**Table 1**). Oral aripiprazole should be given in conjunction with the first injection of aripiprazole lauroxil for 21 consecutive days.[12]

The aripiprazole lauroxil extended-release injectable suspension is available in 3 strengths, including 441 mg in 1.6 mL, 662 mg in 2.4 mL, and 882 mg in 3.2 mL. Each kit contains a 5-mL prefilled syringe containing aripiprazole lauroxil in a sterile aqueous suspension, as well as safety needles.[12]

Pivotal Clinical Trial

The approval of aripiprazole lauroxil in schizophrenia was based on the results of a 12-week, randomized, double-blind, placebo-controlled, fixed-dose phase 3 clinical trial in adults who met the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* criteria for schizophrenia.[11,14] A total of 622 patients were enrolled in the study; 207 patients received 441 mg of aripiprazole lauroxil, 208 patients received 882 mg of aripiprazole lauroxil, and 207 patients received placebo.[12]

Table 1 Doses of Aripiprazole Lauroxil Based on Oral Aripiprazole Total Daily Dose

Oral aripiprazole	Intramuscular aripiprazole lauroxil
10 mg daily	441 mg monthly
15 mg daily	662 mg monthly
≥20 mg daily	882 mg monthly

Source: Aristada (aripiprazole lauroxil) injection prescribing information; January 2016.

Table 2 Efficacy Results of Aripiprazole Lauroxil in Schizophrenia

PANSS total score	Aripiprazole lauroxil 441 mg	Aripiprazole lauroxil 882 mg	Placebo
Baseline score, mean (SD)	92.6 (10.2)	92.0 (10.8)	93.9 (11.3)
Least-squares change from baseline, mean (SE)	–20.9 (1.4)	–21.8 (1.4)	–9.8 (1.4)
Placebo-subtracted difference[a]	–10.9 (95% CI, –14.5 to –7.3)	–11.9 (95% CI, –15.4 to –8.3)	N/A

[a]Difference (drug minus placebo) in least-squares mean change from baseline.
CI indicates confidence interval, not adjusted for multiple comparisons; N/A, not applicable; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation; SE, standard error.
Source: Aristada (aripiprazole lauroxil) injection prescribing information; January 2016.

After establishing tolerability to oral aripiprazole, patients received oral aripiprazole or placebo daily for the first 21 days. Intramuscular injections of aripiprazole lauroxil were administered on days 1, 29, and 57.[12]

The efficacy of aripiprazole lauroxil was assessed using the Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impression (CGI) improvement scale.[12] PANSS is a 30-item scale that measures the positive and negative symptoms of schizophrenia (14 items) and general psychopathology (16 items). Each item is rated on a scale of 1 (absent) to 7 (extreme), such that the PANSS scores range from 30 to 210.[12,14] The CGI improvement scale rates improvement in mental illness on a scale of 1 (very much improved) to 7 (very much worse).[12,14]

Patients ranged in age from 18 to 70 years, and their PANSS total scores ranged from 70 to 120.[12] The patients' PANSS scores were ≥4 for 2 or more of the selected positive scale items. Patients also had to have a CGI severity scale score of ≥4 at baseline.[12]

The primary efficacy variable was the change from baseline to day 85 in the PANSS total score.[12] Significant changes in the PANSS total score were seen with

the 2 doses of aripiprazole lauroxil compared with placebo (**Table 2**).[12,14] At day 85, both aripiprazole lauroxil treatment groups also demonstrated superior CGI improvement scores compared with placebo.[12]

Adverse Reactions

Aripiprazole lauroxil has been evaluated for safety in 880 adult patients with schizophrenia who participated in clinical trials.[12] The most common adverse reactions reported with aripiprazole lauroxil 882 mg and 441 mg at a rate of ≥2% and more often than placebo included akathisia (11%, 11%, 4%, respectively), headache (5%, 3%, 3%), injection-site pain (4%, 3%, 2%), insomnia (4%, 3%, 2%), increased blood creatine phosphokinase levels (1%, 2%, 0%), and increased weight (2%, 2%, 1%).[12]

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Contraindications

Because hypersensitivity reactions ranging from pruritus and urticaria to anaphylaxis can occur after exposure to aripiprazole, aripiprazole lauroxil is contraindicated in patients with a known hypersensitivity reaction to aripiprazole.[12]

Warnings and Precautions

Boxed warning. Aripiprazole lauroxil was approved with a boxed warning stating that elderly patients with dementia-related psychosis who receive antipsychotic drugs are at an increased risk for death, and that aripiprazole lauroxil is not approved for the treatment of patients with dementia-related psychosis.[12]

Increased mortality in elderly patients with dementia-related psychosis. Older patients with dementia-related psychosis taking atypical antipsychotics are at increased risk for death compared with placebo. Although the causes of death varied in clinical trials, the majority of deaths were related to cardiovascular or infectious causes.[12]

Cerebrovascular reactions. Elderly patients with dementia who received risperidone, aripiprazole, and olanzapine had higher incidence of cerebrovascular adverse reactions, including fatalities, compared with patients who received placebo.[12]

Neuroleptic malignant syndrome (NMS). NMS is a potentially fatal symptom complex that is associated with antipsychotic drugs, including aripiprazole lauroxil. The management of NMS includes immediate discontinuation of antipsychotic drugs and other drugs that are not essential to concurrent therapy, as well as intensive treatment and medical monitoring. Patients who require antipsychotic agents after recovering from NMS should be closely monitored.[12]

Tardive dyskinesia. Tardive dyskinesia is a syndrome of potentially irreversible, involuntary, dyskinetic movements. The risk for irreversible tardive dyskinesia may increase with increased duration of treatment. However, tardive dyskinesia can also develop after a relatively brief treatment period at low doses. The discontinuation of aripiprazole lauroxil should be considered if symptoms of tardive dyskinesia occur.[12]

Metabolic changes. Atypical antipsychotic drugs are associated with metabolic changes, including hyperglycemia, diabetes mellitus, dyslipidemia, and weight gain. In a long-term, open-label study of aripiprazole lauroxil in patients with schizophrenia, 14% of patients with normal glycated hemoglobin (Hb) A_{1c} levels at baseline developed elevated HbA_{1c} levels during the study period. Shifts in the baseline fasting total cholesterol levels from normal to high (≥240 mg/dL) were reported in 1% of patients.[12] In the pivotal 12-week clinical trial, 10% of patients taking aripiprazole lauroxil 441 mg had a weight gain ≥7% of body weight, as well as 9% of those taking aripiprazole lauroxil 882 mg.[12]

Orthostatic hypertension. Aripiprazole can cause orthostatic hypotension. In a long-term, open-label study, orthostatic hypotension was reported by 1 (0.2%) patient who received aripiprazole lauroxil.[12]

Leukopenia, neutropenia, agranulocytosis. Patients with a history of leukopenia or neutropenia should have frequent complete blood counts for the first few months of therapy. Aripiprazole lauroxil should be discontinued if severe neutropenia occurs.[12]

Seizures. Aripiprazole lauroxil should be used with caution in patients with a history of seizures, or with conditions that lower the seizure threshold.[12]

Potential for cognitive and motor impairment. Similar to other antipsychotics, the use of aripiprazole lauroxil can impair judgment, thinking, and motor skills.[12]

Body temperature regulation. Appropriate monitoring is recommended when aripiprazole lauroxil is prescribed to patients with conditions that can contribute to an elevation in the core body temperature.[12]

Dysphagia. Aripiprazole lauroxil should be used with caution in patients at risk for aspiration pneumonia.[12]

Use in Specific Populations

Pregnancy. Published data regarding the use of aripiprazole in pregnant women are not sufficient to determine the risk for birth defects or for miscarriage.[12] Extrapyramidal symptoms and withdrawal symptoms have been observed in neonates who were exposed to antipsy-

chotic drugs during the third trimester of pregnancy.[12]

Lactation. Aripiprazole is present in human breast milk.[12] Data are not available regarding the amount of aripiprazole in breast milk, its effects on the breast-fed infant, or its effects on milk production. Clinicians should consider the benefits and the risks of therapy with aripiprazole lauroxil in breast-feeding patients.[12]

Cytochrome (CY) P2D6 poor metabolizers. Adjustment of aripiprazole lauroxil dosing is recommended in patients who are poor metabolizers of CYP2D6.[12]

The FDA approval of aripiprazole lauroxil provides a new effective and safe long-acting treatment option for patients with schizophrenia.

Pediatric use. There are no data to establish the safety of aripiprazole lauroxil in pediatric patients.[12]

Geriatric use. There are no data to establish the safety of aripiprazole lauroxil in patients aged >65 years.[12]

Renal and hepatic impairment. Dosage adjustment of aripiprazole lauroxil is not required for patients with renal or hepatic impairment.[12]

Conclusion

The FDA approval of aripiprazole lauroxil provides a new effective and safe long-acting treatment option for patients with schizophrenia. Clinical data demonstrate that aripiprazole lauroxil extended-release injectable suspension is an effective and safe alternative for the treatment of adults with schizophrenia. Compared with other long-acting injections for these difficult-to-treat patients, aripiprazole lauroxil offers 2 dose options (eg, every 4 weeks, every 6 weeks) and prefilled syringes. ■

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